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ISSN: 0973-4945; CODEN ECJHAO  
E-Journal of Chemistry  
2009, 6(2), 545-552

## Kinetics of Oxidation of Metochlopramide with Chloramine-T in $\text{HClO}_4$ Medium

K. M. MEENAKSHI and K. VASANT KUMAR PAI\*

Department of Industrial Chemistry,  
Kuvempu University, Shankaraghatta,  
Shimoga-577451, India.  
*drkvpai@yahoo.com*

Received 1 October 2008; Accepted 12 December 2008

**Abstract:** The kinetics of oxidation of metochlopramide hydrochloride (MCP) with sodium *N*-chloro *p*-toluenesulfonamide (CAT) in perchloric acid solution has been studied at 313K. The reaction rate shows a first order dependence on [CAT], fractional order on [MCP] and inverse fractional order on  $[\text{H}^+]$ . There is a negative effect of dielectric constant of the solvent. The addition of the reduction product of CAT has no significant effect on the rate. The rate remained unchanged with the variation in the ionic strength of the medium. The reaction fails to induce the polymerization of acrylonitrile. Thermodynamic parameters have been computed by Arrhenius plot. The stoichiometry of the reaction was found to be 1:2 and oxidation products were identified. The Michaelis-Menten type of kinetics has been proposed.  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCl}$  have been assumed to be the reactive oxidizing species. Thermodynamic parameters were computed by studying reactions at different temperatures. A mechanism consistent with observed kinetics is proposed.

**Keywords:** Oxidation, Kinetics, Metochlopramide, Chloramine-T, Perchloric acid medium.

### Introduction

Metochlopramide hydrochloride (MCP) is a frequently prescribed drug in adults and children as an anti-emetic activity with limited local anesthetic properties<sup>1</sup>. Metochlopramide was found to possess central dopamine antagonist properties, and subsequently has been shown to be antipsychotic<sup>2</sup> and for preventing vomiting induced by antineoplastic drugs<sup>3</sup>. In addition, it has been widely used as gastrointestinal (GI) prokinetic drug for gastro esophageal reflux disease, dyspepsia, and diabetic gastroparesis<sup>4</sup>. Kinetic study of the Maillard reaction between metochlopramide hydrochloride and lactose has reported by Zhihui Qiu *et al*<sup>5</sup>.

Anodic stripping voltammetric determination of metoclopramide has reported by Farghaly, O. A. *et al.*<sup>6</sup>. Different parameters such as medium, supporting electrolyte, pH, accumulation potential, scan rate, accumulation time and ionic strength, were tested to optimize the conditions for the determination of MCP. The data obtained are compared with the standard official method.

A review of the literature shows that kinetics of oxidation of the title compound using CAT has not been reported. Hence it was found interesting to investigate the title reaction. Therefore in the present communication we report an investigation of the kinetic and mechanistic aspects of the oxidation of MCP with chloramine-T in HClO<sub>4</sub> at 313K.

## Experimental

Chloramine-T (E. Merck) was purified by the method of Morris *et al.*<sup>7</sup>. Aqueous solutions of the oxidants were standardized by the iodometric method and preserved in brown bottles to prevent photochemical deterioration. MCP (IPCL Ltd., India) was used without further purification. Aqueous solutions of desired strength were prepared freshly each time. All other reagents used were of analytical grade. The ionic strength of the reaction mixture was kept at a high value ( $\mu = 0.5 \text{ mol dm}^{-3}$ ) using a concentrated solution of sodium per chlorate. Permittivity (dielectric constant, D) of the reaction medium was altered by the addition of methanol in varying proportions (v/v). Double distilled water was used throughout these kinetic reactions.

### *Kinetic measurements*

The reactions were carried out under pseudo first-order conditions by keeping an excess of metochlopramide over CAT. Solutions containing appropriate amounts of MCP, NaClO<sub>4</sub>, acid and water (to keep the total volume constant for all runs) were taken in a glass-stoppered Pyrex boiling tube, and thermostated at 313K. A measured amount of CAT solution, also thermostated at the same temperature, was rapidly added to the mixture. The progress of the reaction was monitored by iodometric estimation of unreacted CAT in a measured aliquot of the reaction mixture at different time intervals. The course of the reaction was studied up to 75 to 80% completion. The rate constants were evaluated from the plots of log [CAT] against time. The pseudo first-order rate constants calculated were reproducible within  $\pm 4\%$ .

### *Stoichiometry and product analysis*

Reaction mixtures containing varying ratios of CAT to MCP in the presence of HClO<sub>4</sub> were equilibrated at 313K for 48 h. Estimation of un-reacted CAT showed that one mole of MCP consumed two moles of oxidant, confirming the following stoichiometry



Where, R = CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>.

The oxidation product 2-(4-amino-5-chloro-2-methoxybenzamido) acetic acid is identified by the spot tests. Further the product is confirmed by IR and GC-MS spectral analysis. IR spectral bands of the product observed are 3445 cm<sup>-1</sup>(N-H stretch); 3190 cm<sup>-1</sup>(CONH<sub>2</sub>); 2810 cm<sup>-1</sup>(CH<sub>2</sub>); 1693 cm<sup>-1</sup>(C=O); 3468 cm<sup>-1</sup>(-OH), and 3366 cm<sup>-1</sup> and 3234 cm<sup>-1</sup>(-NH<sub>2</sub>); Aromatic C-H stretch, 3070, 3030 cm<sup>-1</sup>. It was further confirmed by mass spectrum, where the mass spectrum showed a molecular ion peak at 258 amu clearly confirms the identity of the product. The other oxidation product diethyl amine is identified by spot tests. It was also observed that there was no further oxidation of these products under the present kinetic conditions.

*p*-Toluenesulfonamide ( $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$ ), the reduction product of CAT was also extracted with ethyl acetate and identified by TLC<sup>8</sup> using petroleum ether-chloroform-1-butanol (2:2:1 v/v) as the solvent system and iodine as spray reagent ( $R_f = 0.84$ ). Further, the molecular ion peak of 171 amu clearly confirms *p*-toluenesulfonamide (PTS). All other peaks observed in GC-MS are to be interpreted in accordance with the observed structure.

## Results and Discussion

The oxidation of MCP by CAT in perchloric acid medium has been kinetically investigated at different initial concentrations of the reactants in the presence of  $\text{HClO}_4$  at 313 K.

### *Effect of varying reactant concentrations on the rate*

With the substrate in excess ( $[\text{MCP}] \gg [\text{CAT}]$ ), at constant  $[\text{HClO}_4]$ ,  $[\text{MCP}]$ , and temperature, the  $[\text{CAT}]_0$  was varied. Plots of  $\log [\text{CAT}]$  versus time were linear ( $r > 0.986$ ) indicating a first-order dependence of the rate on  $[\text{CAT}]_0$ . The pseudo first-order rate constants ( $k'$ ) calculated from the slopes are given in Table 1. The values of  $k'$  are unaltered with variation of  $[\text{CAT}]_0$  confirming the first-order dependence of the rate on  $[\text{CAT}]$ . Under similar experimental conditions, an increase in  $[\text{MCP}]_0$  increased the  $k'$  values (Table 1). Plot of  $\log k'$  versus  $\log [\text{MCP}]$  was linear (Figure 1;  $r = 0.998$ ) with a slope of 0.42 indicating a fractional-order dependence on  $[\text{MCP}]_0$ .

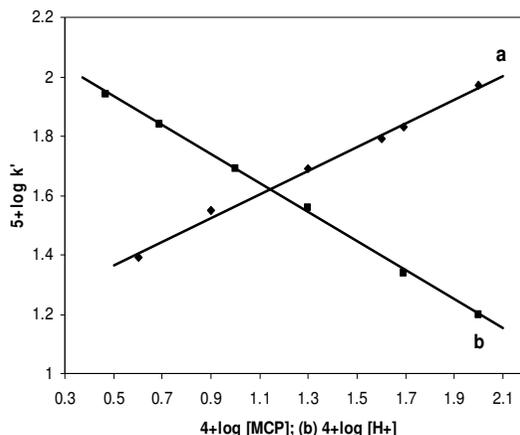
**Table 1.** Effect of varying concentrations of oxidant, substrate and acid on the reaction rate constant.

$10^4[\text{CAT}]$ mol dm <sup>-3</sup>	$10^3[\text{MCP}]$ mol dm <sup>-3</sup>	$10^3[\text{HClO}_4]$ mol dm <sup>-3</sup>	$k' \cdot 10^4$ s <sup>-1</sup>
2.0	2.0	1.0	5.10
4.0	2.0	1.0	5.15
6.0	2.0	1.0	5.11
8.0	2.0	1.0	5.08
2.0	0.4	1.0	2.52
2.0	0.8	1.0	3.20
2.0	4.0	1.0	6.31
2.0	5.0	1.0	6.90
2.0	10.0	1.0	9.40
2.0	2.0	0.3	8.80
2.0	2.0	0.5	7.00
2.0	2.0	2.0	3.70
2.0	2.0	5.0	2.22
2.0	2.0	10.0	1.60
<sup>a</sup> 2.0	2.0	1.0	5.20
<sup>b</sup> 2.0	2.0	1.0	5.10
<sup>c</sup> 2.0	2.0	1.0	5.10

$\mu = 0.5 \text{ mol dm}^{-3}$ , a - in presence of *p*-toluenesulfonamide, b - at  $\mu = 1.0 \text{ mol dm}^{-3}$  and c - in presence of NaCl.  $T = 313\text{K}$ .

### *Effect of varying $[\text{H}^+]$ on the rate*

The  $[\text{H}^+]$  was varied using  $\text{HClO}_4$ . The rate decreased with increase in  $[\text{H}^+]$  (Table 1). A plot of  $\log k'$  versus  $\log [\text{H}^+]$  was linear (Figure 1;  $r = 0.998$ .) with a negative slope of 0.47 indicating an inverse fractional-order dependence of rate on  $[\text{H}^+]$ .



**Figure 1.** Plot of  $5+\log k'$  versus (a)  $4+\log [\text{MCP}]$ ; (b)  $4+\log [\text{H}^+]$ .

#### *Effect of halide ions on the rate*

At constant  $[\text{H}^+]$ , addition of  $\text{Cl}^-$  in the form of  $\text{NaCl}$  ( $1 \times 10^{-3}$ – $8 \times 10^{-3}$  mol  $\text{dm}^{-3}$ ), had no significant effect on the rate of reaction.

#### *Effect of added *p*-toluene sulfonamide on the rate*

The addition of reduced product of oxidant, *p*-toluene sulfonamide ( $1 \times 10^{-3}$ – $8 \times 10^{-3}$  mol  $\text{dm}^{-3}$ ) had no significant effect on the rate indicating that, it is not involved in pre-equilibrium step.

#### *Effect of varying ionic strength and dielectric permittivity of the medium on the rate*

The reaction rate remained unaffected upon varying ionic strength of the medium by the addition of  $\text{NaClO}_4$  (0.1 - 0.8 mol  $\text{dm}^{-3}$ ). The dielectric permittivity of the medium was varied by adding different proportions (0 - 40 %, v/v) of methanol to the reaction mixture. The rate decreased with decrease in dielectric permittivity of the reaction mixture (Table 2). The plot of  $\log k'$  versus  $1/D$  ( $r=0.973$ ), where  $D$  is the dielectric permittivity of the medium ( $D$  values are taken from the literature<sup>9-11</sup>), gave a straight line with a negative slope. Blank experiments showed that methanol was not oxidized by CAT under the experimental conditions employed.

**Table 2.** Effect of Variations of ionic strength on the reaction rate.

Methanol, %, v/v	$10^2/D$	$10^4 k, \text{s}^{-1}$
0.0	1.30	5.10
10.0	1.38	4.00
20.0	1.48	3.30
30.0	1.60	2.35
40.0	1.72	1.40

$[\text{CAT}] = 2 \times 10^{-4}$  mol  $\text{dm}^{-3}$ ;  $[\text{MCP}] = 2 \times 10^{-3}$  mol  $\text{dm}^{-3}$ ;  $[\text{HClO}_4] = 1 \times 10^{-3}$  mol  $\text{dm}^{-3}$ ;  $\mu = 0.5$  mol  $\text{dm}^{-3}$

#### *Effect of varying temperature on the rate*

The reaction was studied at different temperatures (303–323 K) keeping other experimental conditions constant (Table 3). From the linear Arrhenius plot of  $\log k'$  versus  $1/T$  (Figure 3;  $r=0.994$ ), the activation energy and other thermodynamic parameters for the composite reaction and rate limiting step were computed. These are given in Table 3.

**Table 3.** Effect of temperature on the reaction rate and activation parameters.

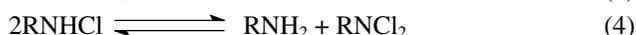
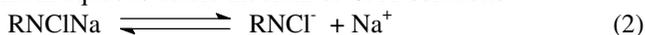
Temperature, K	$10^4 k_1, s^{-1}$	$10^4 k_3, s^{-1}$	Activation parameters
303	2.60	(4.84)	$E_a, kJ mol^{-1}$ 55.65(46.10)
308	3.74	(6.90)	$\Delta H^\ddagger, kJ mol^{-1}$ 53(43.68)
313	5.10	(9.69)	$\Delta S^\ddagger, JK^{-1} mol^{-1}$ -140(134.5)
318	7.60	(16.70)	$\Delta G^\ddagger, kJ mol^{-1}$ 96.82(94.20)
323	10.4	(19.20)	-

Note. Values in parenthesis are the decomposition constants and activation parameters for the rate-limiting step.

### Test for free radicals

The addition of aqueous acrylonitrile solution to the reaction mixture in an inert atmosphere did not initiate polymerization, indicating the absence of free radical species in reaction sequence.

Chloramine-T acts as mild oxidant in both acidic and alkaline medium. In general, CAT undergoes a two-electron change in its reactions forming the reduced products, PTS ( $CH_3C_6H_4SO_2NH_2$ ) and sodium chloride. The oxidation potential of CAT-PTS red-ox couple varies with pH of the medium 1.139V at pH 0.65, 0.778V at pH 7.0 and 0.614V at pH 9.7. Bishop and Jennings<sup>12</sup>, Hardy and Johnston<sup>13</sup>, Morris *et al*<sup>8</sup> and Pryde and Soper<sup>14</sup> have formulated the following equilibria in aqueous acidic medium of CAT solutions

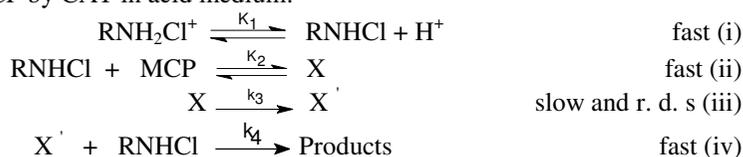


Where R =  $CH_3C_6H_4SO_2$ .

The possible oxidizing species in acidified CAT solutions are therefore RNHCl,  $RNCl_2$  and HOCl. If  $RNCl_2$  were to be the reactive species then from (4) the rate law should predict a second order dependence of rate on  $[CAT]_0$ , which is not observed at the present experimental conditions. Further (6) indicates that hydrolysis is slight and if HOCl is primarily involved a first order retardation of the rate by the added *p*-toluenesulfonamide is expected. However no such effect was noticed. It is therefore, probable that RNHCl is the reactive species. Further protonation of RNHCl at pH<2 according to equation (8) has been reported<sup>15-16</sup>.



Where, when R = *p*- $CH_3C_6H_5SO_2$ -,  $K = 1.02 \times 10^2$  at 25 °C, while with R =  $C_6H_5SO_2$ -,  $K = 61 \pm 5$  at 25 °C. In the present investigations, the retardation of rate by  $H^+$  ion indicates that the unprotonated oxidant (RNHCl) is the active oxidizing species. Based on the preceding discussion the following scheme 1, is proposed to account the observed kinetics for the oxidation of MCP by CAT in acid medium:



**Scheme 1.**



Substituting equation (12) in equation (9), the following rate law can be obtained:

$$\text{rate} = -\frac{d[\text{CAT}]}{dt} = \frac{K_1 K_2 k_3 [\text{CAT}]_i [\text{MCP}]}{[\text{H}^+] + K_1 (1 + K_2 [\text{MCP}])} \quad (13)$$

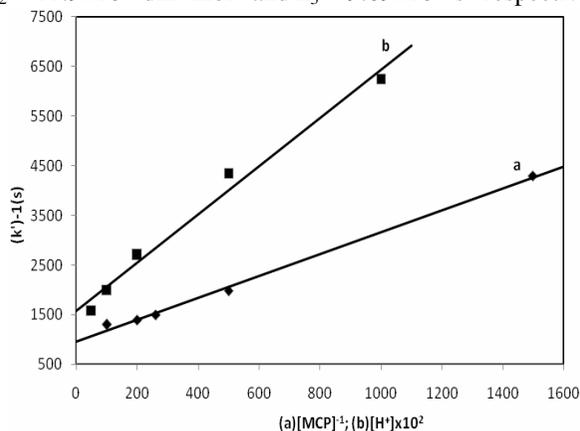
Rate law (13) is in agreement with the experimental results, where a first order dependence of rate on [CAT], a fractional order on [MCP] and an inverse fractional order in  $[\text{H}^+]$  have been noted.

Since  $\text{rate} = k' [\text{CAT}]_i$ , equation (13) can be transformed into equations (14)-(15)

$$k' = \frac{K_1 K_2 k_3 [\text{MCP}]}{[\text{H}^+] + K_1 (1 + K_2 [\text{MCP}])} \quad (14)$$

$$\frac{1}{k'} = \frac{1}{K_2 K_3 [\text{MCP}]} \left( \frac{[\text{H}^+]}{K_1} + 1 \right) + \frac{1}{k_3} \quad (15)$$

Based on equation (15), plots of  $1/k'$  versus  $1/[\text{MCP}]$  and  $1/k'$  versus  $[\text{H}^+]$  were found to be linear (Figure 2). From the slopes and intercepts of these plots, values of formation constants  $K_1$  and  $K_2$  and decomposition constant  $k_3$  were calculated and found to be  $K_1 = 3 \times 10^{-3} \text{ mol dm}^3$ ;  $K_2 = 11.9 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1}$  and  $k_3 = 9.69 \times 10^{-4} \text{ s}^{-1}$  respectively.



**Figure 2.** Plot  $1/k'$  versus (a)  $[\text{MCP}]^{-1}$ ; (b)  $[\text{H}^+]$

Since the rate was fractional in  $[\text{MCP}]_0$ , the Michaelis-Menten kinetics<sup>17</sup> was adopted to study the effect of  $[\text{MCP}]_0$  on rate at different temperatures, by plotting  $1/k'$  versus  $1/[\text{MCP}]_0$ . Using the calculated  $k_3$  values, activation parameters for the rate-limiting step were computed from the linear Arrhenius plot of  $\log k_3$  versus  $1/T$  (Figure 3). These data are presented in Table 3.

The effect of solvent on the reaction kinetics has been described by Laidler<sup>17</sup> and Amis<sup>18</sup>. In the present investigation, a plot of  $\log k'$  versus  $1/D$  was linear with a negative slope. This observation indicates the ion-dipole nature of the rate determining step in the reaction sequence and also points to extending of charge to the transition state.

The rate of the reaction is unaltered by the added PTS showing that it is not involved in a pre-equilibrium. The variation of ionic strength of the medium does not alter the rate. The proposed mechanism is also supported by the moderate values of energy of activation and other thermodynamic parameters (Table 3). The moderate value of  $\Delta H^\ddagger$  and the high negative value of  $\Delta S^\ddagger$  indicate that, the transition state is more ordered than the reactants.

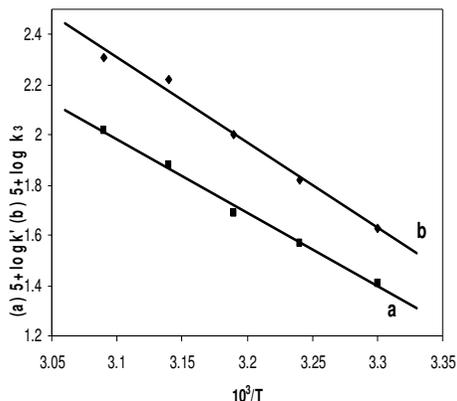


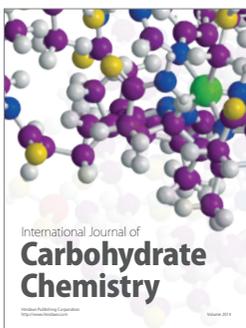
Figure 3. A Plot of  $10^3/T$  versus (a)  $5+\log k'$  (b)  $5+\log k_3$

## Conclusions

Oxidation of MCP with CAT in  $\text{HClO}_4$  medium has been studied. The stoichiometry of oxidation of MCP with CAT in acid medium is found to be 1:2. The oxidation products were identified 2-(4-amino-5-chloro-2-methoxybenzamido) acetic acid and diethyl amine. The active oxidizing species involved in the acid medium is  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCl}$ . Activation parameters were computed from the Arrhenius plot. The observed results have been explained by plausible mechanism and the related rate laws has been deduced.

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